

REMARKS

Status of Claims.

Claim 10 is currently amended;
Claims 1-9 and 18-19 are canceled;
New claim 24 is added;
Claims 10-13, 15-17, and 20-24 are pending in the application.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

In the Office Action, claims 10-13, 15-17 and 20-23 are rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, it is alleged that, as broadly and openly described, “stretches of identical nucleotides” recited in the claims are not limited to 4-5 or 8-10 identical nucleotides (e.g., adenosine), but are open to an infinite number of identical nucleotides and, therefore, one of ordinary skill in the art cannot ascertain the metes and bounds set forth by the language “stretches of identical nucleotides” in the claims, thereby rendering the claims indefinite.

In reply, Applicants respectfully submit that one skilled in the art would be able to appreciate the metes and bounds of the identical nucleotides as set forth in currently amended claim 10. Claim 10 now recites that “each said insulator sequence comprises a polynucleotide consisting of identical nucleotides.” Claim 10, as currently amended, further requires that each insulator sequence also comprises “identical restriction sites flanking said polynucleotide.” Claim 10 further requires that the at least one “insulator” sequence not only separates the RNA “tags” and the RNA “target,” but at the same time functions to ensure proper folding of the RNA tags and to discourage interaction between the RNA “tags” and the “target” RNA. These amendments are supported in the specification at page 15, lines 22-30, for example. As explained in the attached *Declaration of Henry M. Krause*, one of skill in the art would have understood at the time of the invention that an insulator sequence “polynucleotide” would have a finite length, and the artisan would have understood that the functional limitations recited in claim 10 would also necessarily limit the length of the insulator sequences. It would have also

been understood that the length of the selected insulator sequence polynucleotide would vary depending on the nature of the particular RNA tags and target RNA selected for a given application. The functional limitations of claim 10 are consistent with the provisions of MPEP 2173.05(g).

In conjunction with the current amendment of claim 10, new dependent claim 24 is added to recite that the polynucleotide is a sequence of 4–10 identical nucleotides. This claim is supported in the specification at page 15, lines 25 and 28; page 18, lines 18–20; and Fig. 1C, for example.

Claims 10–13, 15–17 and 20–23 are also rejected in the Office Action as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. Claim 10 is currently amended to clarify the relationship between the recited elements. The amended claim clarifies that the at least two different RNA tags are located at the 5' and/or 3' ends of the target RNA sequence and that the at least one insulator sequence separates the target RNA sequence and the RNA tags. Clearly, the insulator sequence comprises two identical restriction sites and a polynucleotide of identical nucleotides is located between those two restriction sites. Support for this amendment is found in Figs. 1A and 1C of the specification, for example.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 10, 12, 15–17 and 20–22 are rejected in the Office Action under 35 U.S.C. § 103(a) as being unpatentable over *Srisawat et al.* in view of *Skerra et al.* (*Biomolecular Engineering*, 1999, 1679–86), *Miki et al.* (U.S. Patent No. 5,595,895) and *Colgin et al.* (*Protein Science*, 1998, 7:667–672). The Office Action acknowledges that *Srisawat et al.* do not teach that the spacer (or insulator) sequence of *Srisawat et al.* comprises identical nucleotides flanked by identical restriction sites, nor do they teach that the RNA tag interacts with a ligand in a reversible fashion. It is alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the RNA fusion molecule of *Srisawat et al.* by incorporating the reversible Strep-tag of *Skerra et al.*, and the SfiI restriction sites

("GGCCNNNNNGGCC") of *Miki et al.*, wherein the SfiI restriction sites comprise the "AAAAA" spacer sequence of *Colgin et al.* in place of the "NNNNN" of the SfiI sequence.

Applicants respectfully traverse this rejection. Claim 10, as currently amended, requires that at least one insulator sequence separates the target RNA sequence and the RNA tags and functions to ensure the proper folding of the RNA tags and to discourage interaction between the RNA tags and the target RNA sequence. Support for this amendment can be found at page 15, lines 22-30 of the specification (which corresponds to paragraph [0102] of the instant U.S. Patent Application Publication No. 2006/0105341).

Skerra et al. describe a protein tagging system composed entirely of amino acids, wherein "[t]he Strep-tag constitutes a nine amino acid-peptide that binds specifically to streptavidin" (pg. 79 of *Skerra et al.*). In marked contrast, the tags described by the Applicants are RNA motifs designed for purifying RNAs (and any associated proteins, if desired). These are completely different systems and address problems that are not directly comparable to the RNA fusion molecules of the instant application. Although there is no teaching or suggestion in *Skerra et al.* of an RNA that encodes streptavidin, the Office Action has nevertheless taken the untenable position that the skilled artisan would have been motivated to replace the S1 or D8 tag of *Srisawat et al.* with the Strep-tag of *Skerra et al.* because *Skerra et al.* taught that the Strep-tag binds its ligand in a reversible fashion and that the Strep-tag is an ideal device for the rapid functional screening of purified gene products in modern proteome research. Applicants respectfully point out that the Office Action is mistakenly combining RNA and protein molecules in its proposed modification of the RNA molecule of *Srisawat et al.* Accordingly, the *Skerra et al.* reference cannot make up for the failure of *Srisawat et al.* to teach a RNA tag that interacts with a ligand in a reversible fashion.

Moreover, combining the teachings of *Miki et al.* with those of *Srisawat et al.* does not cure the failure of *Srisawat et al.* to teach a spacer (or insulator) sequence that comprises identical nucleotides flanked by identical restriction sites. The *Miki et al.* reference discloses DNA sequences and their manipulation by a restriction enzyme. DNA, being double-stranded, is a much different molecule than single-stranded RNA, and the Office Action is again mixing up

different classes of molecules in this proposed modification of the RNA molecule of *Srisawat et al.* It should also be noted that the "GGCCNNNNNGGCC" sequence in *Miki et al.* is the DNA sequence of a SfiI restriction site wherein the "N" nucleotide can be any one of the four nucleotides (col. 11, lines 18–27 of *Miki et al.*). Disposed between a pair of those restriction sites of *Miki et al.* is an exogenous nucleotide sequence which is desired to be excised by a single restriction enzyme (column 11 of *Miki et al.*). The SfiI restriction enzyme cleaves within the central unspecified sequence (col. 11, lines 25–27). Therefore, it can be plainly seen that the NNNNN nucleotide sequence is interior to, and is part of, the restriction sites. The "NNNNN" sequence does not refer to an RNA polynucleotide sequence containing identical nucleotides which are located between a pair of restriction sites.

The *Colgin et al.* reference does not cure the failure of *Miki et al.* to teach an RNA polynucleotide sequence containing identical nucleotides separating a pair of restriction sites. *Colgin et al.* discloses spider silk proteins which contain short (10.7 angstroms) alanine regions (AAAAA) (page 671, second column, last paragraph, through page 672, first column). It is well known to those of skill in the art that alanine is an amino acid building block of protein molecules, not of DNA or RNA. The Office Action is mistakenly combining DNA and amino acids in its proposed modification of the restriction site DNA of *Miki et al.* with the AAAAA alanine domain of *Colgin et al.*

The Office Action takes the position that one of ordinary skill in the art would have been motivated to modify the structure of RNA fusion molecules of *Srisawat et al.* in view of the combined teachings of *Srisawat et al.*, *Skerra et al.*, *Miki et al.* and *Colgin et al.*, because *Srisawat et al.* expressly taught major factors to consider with regard to the specificity of RNA affinity tags (pages 157 and 159). As explained in the attached *Declaration of Henry M. Krause*, identifying a problem and understanding major factors regarding the specificity of RNA affinity tags does not necessarily make the solution to the problem obvious. Additionally, there is no guidance in any of the cited references as to how their incompatible teachings regarding DNA and protein sequences could actually be combined to provide the claimed RNA fusion molecules. Moreover, for the reasons stated above, one of ordinary skill in the art would have had no

reasonable expectation of success in achieving the claimed fusion molecules because the fusion molecule resulting from the proposed combinations would have been, at best, a mixture of RNA, DNA and amino acids.

With respect to claim 23, even if the teachings of *Johansson et al.* as to MS2 coat protein and RNA hairpins, and the teachings of *Bardwell et al.* as to RNA tag purification using two tandem RNA tags were combined with the teachings of *Srisawat et al.*, *Skerra et al.*, *Miki et al.* and *Colgin et al.* as applied to claims 10-13, 15-17 and 20-22, above, this would not make up for the above-described failure of the combined teachings of *Srisawat et al.*, *Skerra et al.*, *Miki et al.* and *Colgin et al.* to teach the RNA fusion molecule of claim 10 (from which claim 23 depends).

Conclusion

Applicants respectfully request withdrawal of the rejections and allowance of the pending claims. If the Examiner feels that a telephone conference might expedite the resolution of any issue that may remain in this case, the Examiner is invited to contact the undersigned.

In the course of the foregoing discussions, Applicants may have at times referred to claim limitations in shorthand fashion, or may have focused on a particular claim element. This discussion should not be interpreted to mean that the other limitations can be ignored or dismissed. The claims must be viewed as a whole, and each limitation of the claims must be considered when determining the patentability of the claims. Moreover, it should be understood that there may be other distinctions between the claims and the prior art that have yet to be raised, but which may be raised in the future.

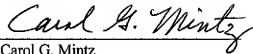
It is believed that no extensions of time or fees are required beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that an extension of time is necessary to allow consideration of this paper, such extension is hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required (including fees for net addition of claims) are hereby authorized to be charged to Deposit Account No. 03-2769 (ref. 1889-00900) of Conley Rose, P.C., Houston, Texas.

Appl. No. 10/531,095

Response to Office Action Mailed November 13, 2007

Amendment Dated March 12, 2008

Respectfully submitted,

A handwritten signature in cursive script that reads "Carol G. Mintz". The signature is written in black ink and is positioned above a horizontal line.

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